Dobutamine magnetic resonance imaging as a predictor of myocardial functional recovery after revascularisation

R J Trent, G D Waiter, G S Hillis, F I McKiddie, T W Redpath, S Walton

Abstract

Objective—To assess the use of dobutamine magnetic resonance imaging (MRI) as a preoperative predictor of myocardial functional recovery after revascularisation, comparing wall motion and radial wall thickening analyses by observer and semi-automated edge detection.

Patients—25 men with multivessel coronary disease and resting wall motion abnormalities were studied with preoperative rest and stress MRI.

Main outcome measures—Observer analysis for radial wall thickening was compared with a normal range, while wall motion analysis used a standard four point scale. Semi-automated analysis was performed using an edge detection algorithm. Segments displaying either improved or worsened thickening or motion with dobutamine were considered viable. Postoperative rest images were performed 3–6 months after coronary artery bypass grafting (CABG) for comparison.

Results—For observer analysis the values for sensitivity and specificity were 50% and 72% for wall motion, with respective values of 50% and 68% for thickening. With semi-automated edge detection the figures for motion were 60% and 73%, with corresponding values of 79% and 58% for thickening. Combining thickening and motion for the semi-automated method to describe any change in segmental function yielded a sensitivity of 71% and specificity of 70%.

Conclusions—Dobutamine MRI is a reasonably good predictor of myocardial functional recovery after CABG. The use of semi-automated edge detection analysis improved results.

(Heart 2000;83:40–46)

Keywords: dobutamine, magnetic resonance imaging myocardial viability; coronary artery bypass grafting
Table 1  Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Infarct site</th>
<th>LVEF % (pre/post)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>M</td>
<td>Anterior</td>
<td>42/45</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>M</td>
<td>Anterior/ inferior</td>
<td>38/19</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>M</td>
<td>Inferior</td>
<td>66/65</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>M</td>
<td>Inferior</td>
<td>63/65</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>M</td>
<td>Inferior</td>
<td>39/43</td>
</tr>
<tr>
<td>6</td>
<td>71</td>
<td>M</td>
<td>Anterior</td>
<td>43/26</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>M</td>
<td>Anterior</td>
<td>52/38</td>
</tr>
<tr>
<td>8</td>
<td>69</td>
<td>M</td>
<td>Anterior</td>
<td>47/34</td>
</tr>
<tr>
<td>9</td>
<td>78</td>
<td>M</td>
<td>Inferior</td>
<td>47/35</td>
</tr>
<tr>
<td>10</td>
<td>71</td>
<td>M</td>
<td>Anterior/ inferior</td>
<td>68/64</td>
</tr>
<tr>
<td>11</td>
<td>68</td>
<td>M</td>
<td>Inferior</td>
<td>56/44</td>
</tr>
<tr>
<td>12</td>
<td>63</td>
<td>M</td>
<td>Anterior</td>
<td>57/46</td>
</tr>
<tr>
<td>13</td>
<td>56</td>
<td>M</td>
<td>Inferior</td>
<td>50/55</td>
</tr>
<tr>
<td>14</td>
<td>41</td>
<td>M</td>
<td>Inferior</td>
<td>48/39</td>
</tr>
<tr>
<td>15</td>
<td>67</td>
<td>M</td>
<td>Inferior</td>
<td>84/73</td>
</tr>
<tr>
<td>16</td>
<td>60</td>
<td>M</td>
<td>Inferior</td>
<td>47/33</td>
</tr>
<tr>
<td>17</td>
<td>67</td>
<td>M</td>
<td>Inferior</td>
<td>46/55</td>
</tr>
<tr>
<td>18</td>
<td>67</td>
<td>M</td>
<td>Anterior</td>
<td>65/70</td>
</tr>
<tr>
<td>19</td>
<td>72</td>
<td>M</td>
<td>Inferior</td>
<td>75/64</td>
</tr>
<tr>
<td>20</td>
<td>66</td>
<td>M</td>
<td>Anterior</td>
<td>54/60</td>
</tr>
<tr>
<td>21</td>
<td>67</td>
<td>M</td>
<td>Inferior</td>
<td>32/46</td>
</tr>
<tr>
<td>22</td>
<td>66</td>
<td>M</td>
<td>Inferior</td>
<td>17/19</td>
</tr>
<tr>
<td>23</td>
<td>56</td>
<td>M</td>
<td>Anterior</td>
<td>29/46</td>
</tr>
<tr>
<td>24</td>
<td>79</td>
<td>M</td>
<td>Anterior</td>
<td>20/34</td>
</tr>
<tr>
<td>25</td>
<td>64</td>
<td>M</td>
<td>Inferior</td>
<td>67/63</td>
</tr>
</tbody>
</table>

Mean (SD) 64 (8.7)

Study images were obtained from baseline to left ventricular apex. Preoperative rest and stress images were performed sequentially, using a dobutamine infusion titrated (mean (SD) dose 15 (4.9) µg/kg/min) to induce a 50% increase in mean basal heart rate from 65 (13) beats per minute to 95 (11) beats per minute. The mean duration of in-scanner time was approximately 30 minutes.

ANALYSIS

Images were studied by three independent observers: a cardiologist (observer 1) and two medical physicists from the MRI department. Dysfunctional segments were identified for each subject from the preoperative scans and these segments were then characterised as viable/non-viable on the basis of the response to dobutamine. These data were then tested against the postrevascularisation results; interpretation of postoperative resting MR images was performed blinded to the results of the dobutamine study and in a random manner. Calculation of sensitivity and specificity was performed from standard formulae. This was done for all abnormal segments, and also broken down into akinetic (score 1) and hypokinetic (score 2) segments, as there is some evidence to suggest that the predictive power of dobutamine (echo) is greatest in the most severely dysynergic segments.

MRI data were analysed from four short axis views divided into a six segment “cartwheel” (fig 1). Left ventricular wall thickness was measured in the centre of each segment, perpendicular to the epicardium. Manual measurement of radial wall thickening was made with electronic calipers and compared with the existing normal range for this centre (n = 31, table 2), a reduction of > 1 SD below normal being considered as reduced. A value of > 1 SD was used because of the large variation in the normal database. Semisubjective regional wall motion observer analysis was scored on a scale of 0–3 (0 = dyskinesis; 1 = akinesis; 2 = hypokinesis; 3 = normal) and a reduced regional wall motion as a score of ≤ 2. Global left ventricular function was not formally assessed as a criterion of study entry, but was measured incidentally as the LVEF pre- and postoperatively by MRI.

Data were also analysed by semi-automated edge detection. After identification of the left ventricular centre point, a radial search at 2° intervals determined the point of maximum pixel intensity gradient, taken as the radial distance of the border from the centre point. Data were then converted into x and y coordinates for epicardial/endoocardial borders, and fitted to a two dimensional polynomial function (degree = 6), allowing interpolation of missing or misrepresented regions. Wall thickness was given by the distance between the interpolated borders at points corresponding to those used in the manual method. Semi-automated wall thickening measurements were made in the centre of the segment to coincide as closely as possible with the manual measurement, therefore no averaging was done. There was no difference in the normal range for segmental...
thickening determined by the semi-automated method ($p = NS$, paired $t$ test). Endocardial wall motion was defined as the percentage change in the distance from the endocardium to the centre of the left ventricle from end diastole to end systole.

The relation between segmental response to dobutamine and global functional improvement within individuals postoperatively was not assessed during the study period, though retrospective analysis was performed. The mean number of dobutamine viable segments by semi-automated edge detection of systolic wall thickening per patient was related to the change in LVEF postoperatively by linear regression. Also, comparison of the mean number of segments in those subjects with improved LVEF was compared with those subjects without improvement.

**STATISTICS**

A segment was deemed to have abnormal wall thickening if its value was found to be more than 1 SD below the mean value. Sensitivity and specificity of dobutamine MRI was determined using postoperative MRI scans as the gold standard for segmental recovery. Sensitivity, specificity, and diagnostic accuracy were calculated using standard formulas and confidence intervals (CIs) determined at the 95% level. Inter- and intraobserver agreement was determined by calculating the mean (SD) of the difference between wall thickness measurements. $x$ statistics were determined for the difference in observer scoring of wall motion. All other results are presented as mean (SD) (table 3). Comparisons of global left ventricular function (LVEF) between groups were made by paired $t$ test (significance level at $p \leq 0.05$) and by linear regression.

**Results**

The ranges (with 95% CIs) of values obtained for sensitivity and specificity for each individual observer are given in table 3. For further discussion the results of wall motion and thickening analyses for observer 3 are quoted. The results for semi-automated edge detection analysis are given for observer 1 only.

**Table 3 Sensitivity of dobutamine stress MRI for the detection of hibernating by semisubjective observer analysis**

<table>
<thead>
<tr>
<th>Observer</th>
<th>Motion</th>
<th>Thickening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (95% CI)</td>
<td>Specificity (95% CI)</td>
</tr>
<tr>
<td>1</td>
<td>52 (43 to 61) 65 (57 to 73)</td>
<td>70 (63 to 77) 60 (52 to 68)</td>
</tr>
<tr>
<td>2</td>
<td>40 (35 to 45) 89 (79 to 91)</td>
<td>52 (44 to 60) 66 (60 to 72)</td>
</tr>
<tr>
<td>3</td>
<td>50 (44 to 56) 72 (67 to 77)</td>
<td>50 (44 to 56) 68 (62 to 74)</td>
</tr>
<tr>
<td>Mean</td>
<td>48 (42 to 54) 80 (76 to 84)</td>
<td>55 (49 to 61) 65 (60 to 70)</td>
</tr>
<tr>
<td>Semi-automated edge detection</td>
<td>60 (55 to 70) 73 (70 to 76)</td>
<td>79 (75 to 83) 58 (54 to 62)</td>
</tr>
</tbody>
</table>

A total of 588/600 segments (98%) were suitable for wall motion analysis. Of these 278 (47%) had a score of 2 at rest, with 111 (40%) having an improved score with dobutamine stimulation (observer 3). Improved wall motion was seen in 149 (54%) postoperatively. The concordance between a positive test result and subsequent postoperative improvement was poor, however, with a sensitivity and specificity of 50% (75/149) and 72% (93/129), respectively. A total of 131/588 (22%) segments were akinetic or dyskinetic (wall motion score $\leq 1$) at rest. Of these, 61 (47%) showed an improved score with dobutamine stimulation, and 58 (44%) a postoperative improvement. The sensitivity and specificity was 60% (35/58) and 64% (47/73), respectively. A further 42 segments with a resting wall motion score of $\leq 2$ showed a worsening score with dobutamine. Of these, nine segments showed postoperative improvement. Inclusion of these data in the analysis improved the sensitivity obtained (61%) at the expense of worsened specificity (58%).

**WALL THICKENING**

A total of 511/600 segments (85%) were suitable for measurement of regional wall thickening. Of the 511 segments, 267 (52%) showed reduced wall thickening at rest. Of these, 107 (40%) showed improvement with dobutamine stimulation and 118/267 (44%) segments improved postoperatively. The concordance between improved wall thickening and postoperative improvement was, however, once again poor, with a sensitivity of 50% (59/118) and a specificity of 68% (101/149). No data for ischaemic segments were available for wall thickening, as the normal range for wall thickening could not be subdivided into a greater degree of abnormality than $>1$ SD below normal.

**SEMI-AUTOMATED EDGE DETECTION**

Out of 516 segments (86%) suitable for semi-automated edge detection analysis, 227 (43%) had reduced wall motion at rest, with 66 (29%) having an improved score during dobutamine stimulation. Improved wall motion was seen in 48 (21%) postoperatively. The concordance between a positive test result and subsequent postoperative improvement was poor, however, with a predictive sensitivity and specificity of 40% (19/48) and 74% (132/179), respectively. Combination of wall thickening and wall motion data to show any improvement in segmental function revealed a sensitivity of 68/114 (60%) and a specificity of 163/232 (70%).

Of the 516 segments suitable for semi-automated edge detection analysis, 119/516 (23%) segments showed reduced wall thickening at rest. Of these, 71 (60%) showed improvement with dobutamine stimulation and 66/119 (55%) segments improved postoperatively. The concordance between improved wall thickening with dobutamine and postoperative improvement was, however, once again
poor, with a sensitivity of 74% (49/66) and a specificity of 58% (31/53).

Inclusion of segments with an ischaemic response (worsened wall motion) to dobutamine stimulation produced an improved sensitivity for wall motion of 60% (29/48), with no change in specificity of 73% (132/179), and corresponding values of 79% (52/66) and 58% (31/53) for wall thickening. Data for wall thickening were produced from a count of those segments with resting wall motion abnormality (≤1 SD below normal) which became more abnormal (≤2 SD) during dobutamine stimulation. Combination of wall thickening and wall motion data as above, to determine any change in segmental function with dobutamine stimulation, revealed a sensitivity of 71% (81/114) and a specificity of 70% (163/232).

GLOBAL LEFT VENTRICULAR FUNCTION

There was a trend towards a reduction in mean LVEF postoperatively, with a fall from 54% to 46%, though this did not reach significance. There was no demonstrable relation between the number of dobutamine viable segments preoperatively and change in LVEF (r = 0.03) between pre- and postoperative scans (fig 2). Nine out of 25 subjects showed an increased LVEF postrevascularisation. However, analysis of the mean number of dobutamine viable segments preoperatively was not significantly different between these subjects and those with no increase, or decreased ejection fraction (p = 0.40). There was a trend towards a lower preoperative LVEF in those patients showing postoperative improvement (41.8% vs 54.7% in non-improvers), though this did not reach significance (p = 0.14).

OBSERVER VARIABILITY

All images from the 25 patients studied were assessed by three independent observers to allow calculation of interobserver variability. The intraobserver variability was determined by repeated measurement from six of the preoperative images performed by one observer. Radial wall thickness measurements are given as the mean (SD) difference between measurements. The difference in wall motion scores is given by the \( \kappa \) statistic. The results of these comparisons are shown in table 4.

**Table 4: Interobserver and intraobserver variation**

<table>
<thead>
<tr>
<th>Mean difference (cm)</th>
<th>SD (cm)</th>
<th>Segments (n)</th>
<th>Segments for ( \kappa ) (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2</td>
<td>0.06</td>
<td>0.43</td>
<td>3564</td>
</tr>
<tr>
<td>1–3</td>
<td>−0.07</td>
<td>0.50</td>
<td>3564</td>
</tr>
<tr>
<td>2–3</td>
<td>0.13</td>
<td>0.48</td>
<td>3564</td>
</tr>
<tr>
<td>1–1</td>
<td>−0.003</td>
<td>0.38</td>
<td>144</td>
</tr>
</tbody>
</table>

Observer 1, GDW; observer 2, TWR; observer 3, RJT.

Discussion

Reliable preoperative identification of viable myocardium remains the ultimate aim in the management of the patient with severe left ventricular dysfunction and coronary artery disease. Survival can be improved by revascularisation, although the mortality and morbidity of CABG is increased in this group. Notwithstanding the lack of randomised controlled trials, Eitzman and colleagues have shown a mortality benefit from CABG in patients with severe left ventricular dysfunction and multivessel coronary disease in the presence of flow metabolism mismatch at PET. Likewise, Di Carli and colleagues have suggested that prognosis is worse in patients with unrevascularised, PET viable myocardium than in those undergoing revascularisation, or having completed infarction.

The uptake of PET imaging as an investigative tool for clinical, rather than research, use is limited by a lack of availability outside a few centres in Europe and the USA, and other methods are likely to be required for this reason. In a meta-analysis of currently available techniques for prediction of functional recovery after revascularisation in patients with left ventricular dysfunction caused by chronic coronary artery disease, Bax and colleagues describe values for sensitivity of 84% and specificity of 94% for systolic wall thickening with low dose (5–10 µg/kg/min) dobutamine echocardiography from 16 studies.

MRI offers theoretical advantages over echocardiography in the assessment of myocardial viability. Chiefly, the use of objectively defined systolic wall thickening as a measure of viability may be superior to semisubjective observer wall motion analysis. Additionally, wall motion analysis is vulnerable to artefacts resulting from paradoxical septal motion, cardiac translation, and tethering. Baer and colleagues have recently described a sensitivity of 89% and specificity of 94% for systolic wall thickening with low dose dobutamine MRI. Gunning and colleagues, however, describe values much closer to our own, with sensitivity and specificity of 50% and 81% for wall motion, and 45% and 83% for wall thickening, respectively, again using a low dose regimen.

Although the majority of echocardiography based and MRI work has described the use of low dose dobutamine for viability study, a number of studies have suggested the use of higher dobutamine doses may be required to optimise the diagnostic yield. Sawada and colleagues used low (5–10 µg/kg/min) and high dose (30 (10) µg/kg/min) regimens. Of those dyssynergic myocardial segments shown to be

![Figure 2](http://heart.bmj.com/)

*Figure 2* Linear regression of segmental response to dobutamine versus change in left ventricular ejection fraction.
viable at PET, wall motion improved with low dose dobutamine in 70%, though in 30% only at high dose. Sklenar and colleagues found, in experimental work, that a dose of 15 µg/kg/min was required to produce maximal wall thickening after myocardial infarction, while Afridi and colleagues found that administration of both low and high dobutamine doses was necessary to optimise the predictive power of dobutamine echocardiography. Moreover, in the worsening phase of those segments showing a biphasic response, this was usually seen with doses of ≥ 20 µg/kg/min. Similarly, Cornel and colleagues used a combined low (5–10 µg/kg/min) and high dose (< 40 µg/kg/min) regimen, showing that a biphasic response was the only independent predictor of an improved LVEF postrevascularisation.

An intermediate dobutamine dose (mean 15 µg/kg/min) was used in this study, in order to minimise potential underdiagnosis of viability reported with standard low dose regimens and reduce the in-scanner time associated with multiple dose imaging. The development of worsening wall motion abnormality in approximately 10% of already abnormal segments suggests ischaemia, and therefore viability, in these segments. Indeed, the inclusion of segments with worsened wall motion or thickening abnormality post dobutamine improved the sensitivity of MRI in this series, though only in association with the use of semi-automated edge detection analysis. However, a further 8% of abnormal segments at rest MRI, as judged by wall motion, and 12% by wall thickening showed no improvement during dobutamine stimulation, although postoperative improvement was seen. It is possible that these areas may have represented a biphasic response, where the improvement in wall motion occurring at a lower level of dobutamine stimulation is followed by “re-worsening” at higher dose levels, and is therefore not apparent with imaging at a single dose. This phenomenon was not well described at the time of drawing up our study protocol, though with retrospect the lack of multiple dose level imaging is a major limitation.

Earlier work by Cornell and colleagues found that the specificity of low dose dobutamine echocardiography was reduced in mildly dysfunctional segments. Kaul and colleagues have shown similar findings. Our data for observer wall motion analysis are not entirely consistent with these findings, showing a slightly better sensitivity and slightly lower specificity in segments with greater resting wall motion abnormality, with a sensitivity of 50% and specificity of 72% for all abnormal segments, and respective values of 60% and 64% in akinetic or dyskinetic segments. The reason for this is not clear, though the relatively small sample size and difference between the study populations may be contributory factors. Given these differences, and the variation in dobutamine stress protocols, it is hard to draw any further conclusions from this aspect of the study results.

Further explanation of the discrepancy between our results and those of Baer and colleagues may be found in analysis of the respective study populations. It is known that the contractile response to dobutamine stimulation of hibernating myocardium, as defined by flow-metabolic mismatch with PET, is poor, in contrast to stunned myocardium. The majority of subjects in this series had been referred for revascularisation for conventional reasons of symptomatic relief, with or without prognostic implications. Regional wall motion abnormality in this situation may well represent repeated episodes of myocardial stunning, rather than hibernation.

In a study of patients with ischaemic left ventricular dysfunction, Sawada found that the majority of PET viable segments with resting wall motion abnormality had normal perfusion and metabolism, suggesting that stunning, rather than hibernation per se, was the cause of the dysfunction. In addition, improvement in wall motion was approximately twice as likely in those regions with normal perfusion and metabolism (that is, stunned) than in those with reduced tracer uptake or mismatch (that is, hibernating). A biphasic response identified segments with normal perfusion and metabolism in nearly 90% of cases, these being subtended by vessels with 70% stenosis. It is important to note, moreover, that the prevalence of severe global left ventricular dysfunction in this series was low, with only 15% of patients studied having a resting LVEF of < 40%, as determined by MRI at the time of study, with a mean LVEF of 54 (14.5)%. The mean normal value for MRI determined LVEF in our centre is 65 (12.5)%. In contrast, Baer and colleagues studied patients referred to a tertiary centre with significantly greater left ventricular dysfunction (mean LVEF 42%). By Bayesian theory, therefore, the yield obtained in this series is likely to be lower.

Perhaps surprisingly, we found no association between the amount of dobutamine viable myocardium (mean segmental response) and change in LVEF postrevascularisation. This is at variance with Baer and colleagues and again seems most likely to be a manifestation of the comparatively better preoperative left ventricular function in our study population. Interestingly, there was a discernable trend towards lower preoperative LVEF in those patients showing improved postoperative LVEF. These findings are consistent with the dictum that the diagnosis of myocardial viability is of greatest importance in those with significantly impaired left ventricular function.

The results of this series are remarkably similar to those obtained by Gunning and colleagues using a low dose dobutamine protocol, without breath hold imaging and a larger (nine segment) segmental imaging method. Both of these studies show a modest sensitivity, with good specificity for the preoperative prediction of functional recovery after revascularisation in dysfunctional myocardial segments. The results obtained by Baer and colleagues are considerably more impressive, with sensitivity and specificity of around 90%.

Although our dobutamine protocol differed from that of Baer and colleagues, the low dose...
protocol was common to both the Gunning and Baer studies. The technique of rapid breath hold imaging was unique to Baer's series, not being available at the outset of our study. Moreover, they excluded myocardial segments not subtended by a 70% coronary stenosis unlike ourselves, and used high dose nitrates periprocedurally to maximise coronary vasodilation.

Further limitations of this study include the possibility that the time to recovery of dysynergic myocardium after CABG in our subjects may have exceeded the 3–6 month period in which postoperative imaging was performed. Cornell and colleagues showed that individuals showing improved global left ventricular function after revascularisation had incomplete recovery at 3–6 months, with late improvement occurring up to a median of 14 months after CABG in approximately one third of these subjects. Moreover, in the absence of routine postoperative angiography, we were unable to exclude incomplete revascularisation or the occurrence of further native vessel/graft occlusion between the immediate postoperative and second MRI study.

The use of manual quantitative analysis, a factor common to ourselves and Gunning and colleagues, was time consuming, and prone to both inter- and intraobserver variability. Application of semi-automated edge detection analysis improved the sensitivity and specificity of MRI as a predictor of preoperative myocardial viability, and reduced interobserver variability. The occurrence of respiratory motion artefacts, caused by the lengthy imaging time inherent to the FISP sequence, resulted in comparatively poor images for some subjects. This issue can now be eliminated by using segmented k-space breath hold techniques not available on the scanner used at the outset of this study.

Sayad and colleagues have suggested that myocardial tagging may offer advantages, though this technique is also a new development and as yet unsubstantiated.

CONCLUSIONS

In keeping with previous data, we have found dobutamine MRI scanning to be a moderately sensitive, and reasonably specific, predictor of functional recovery after CABG in akinetic or severely hypokinetmic myocardium. The use of semi-automated edge detection improved both the sensitivity and specificity of the technique, and may also reduce observer error. Recent developments in rapid breath hold MRI have shown superior results. These are likely to be further improved by the use of multiple dose imaging regimens as scanning times become progressively shorter.

This work was performed with a grant from the British Heart Foundation.

30. Piggot JD, Kouchousko NT, Oberman A, et al. Late results of surgical and medical therapy for patients with coronary


